In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-947V
Filed: August 30, 2023
PUBLISHED

ERWIN CASAZZA,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Laura Levenberg, Muller Brazil, LLP, Dresher, PA, for petitioner.
Julia Marter Collison, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On July 14, 2017, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[2] alleging that the influenza ("flu") vaccine he received on September 3, 2015, caused him to suffer rheumatoid arthritis ("RA"). (ECF No. 1, p. 1.) On October 9, 2019, petitioner filed an amended petition alternatively alleging the same vaccine had instead caused reactive arthritis. (ECF No. 38.) Ultimately, however, petitioner argues that he has met his burden with respect to RA. (ECF No. 71.) For the reasons discussed below, I now find that petitioner is *not* entitled to compensation.

[1] Because this document contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the document will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] Within this decision, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" with the logical sequence being supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program factfinder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

In this case, petitioner has variously alleged that the flu vaccine caused him to suffer either RA or reactive arthritis. Since neither RA nor reactive arthritis is listed on the Vaccine Injury Table relative to the flu vaccine, petitioner must satisfy the above-described *Althen* test for establishing causation-in-fact.

II. Procedural History

This case was initially assigned to another special master. (ECF No. 4.) Accompanying his petition, petitioner filed medical records marked as Exhibit 1-8 along with an affidavit marked as Exhibit 9. (ECF No. 1.) Additional medical records marked as Exhibits 10-12 were subsequently filed.[3] (ECF Nos. 7, 11.) Respondent filed his Rule 4 Report on May 7,2018. (ECF No. 15.) Respondent concluded that the case is not appropriate for compensation.

Additional medical records marked as Exhibits 14-15 were subsequently filed.[4] (ECF Nos. 19-20.) Petitioner then filed an expert report by rheumatologist/immunologist M. Eric Gershwin, M.D. (ECF No. 21; Ex. 16.) Although petitioner had pleaded his injury as RA, Dr. Gershwin disagreed with that diagnosis and instead opined that petitioner suffered reactive arthritis. (Ex. 16, p. 2.) Dr. Gershwin then set forth a theory as to how the flu vaccine can cause reactive arthritis. (*Id*. at 3-4.)

[3] Exhibit 10 was later stricken and refiled on October 9, 2019. Accordingly, that exhibit is docketed at ECF No. 42.

[4] As with Exhibit 10, Exhibit 14 was later stricken and refiled on October 9, 2029. Accordingly, that exhibit is docketed at ECF No. 42.

Respondent responded with two expert reports by rheumatologist Brendan Antiochos, M.D., and immunologist Penelope Morel, M.D. (ECF Nos. 24-27; Exs. A, C.) Both of respondent's experts opined that petitioner suffered RA rather than reactive arthritis and discussed their opinions that there is insufficient evidence the flu vaccine can cause RA. Petitioner then filed a responsive report by Dr. Gershwin shortly thereafter. (ECF No. 28; Ex. 17.) Dr. Gershwin maintained his view that petitioner suffered reactive arthritis and not RA and further stressed that he did not express any opinion that vaccines can cause RA. (*Id*.)

On December 18, 2018, the special master issued an order noting the discrepancy between petitioner's pleading of RA and Dr. Gershwin's opinion based on reactive arthritis. (ECF No. 29.) Petitioner was ordered to clarify the nature of his claim. (*Id*.) Petitioner later filed an amended petition alleging that his flu vaccine caused him to suffer reactive arthritis, though he acknowledged that some of his medical records indicated his diagnosis is RA.[5] (ECF No. 38.) Petitioner also filed additional medical records marked as Exhibits 18-23. (ECF Nos. 31, 34.) Respondent filed a further report by Dr. Antiochos. (ECF No. 36; Ex. E.) Dr. Antiochos indicated that under the relevant diagnostic standards, petitioner's diagnosis of RA should be considered "definite." (*Id*.)

The special master then held a Rule 5 conference on October 8, 2019. (ECF No. 37.) She advised the parties that in her view the medical records "strongly support" respondent's experts' opinion that petitioner suffers RA. The special master also advised that her preliminary view was that a connection between the flu vaccine and RA is unsupported. (*Id*.) Thereafter, petitioner again filed additional medical records (Ex. 24) and a third report by Dr. Gershwin (ECF Nos. 44-45; Exs. 25-26). In his third report, Dr. Gershwin changed his view based on more recent laboratory testing and agreed with Dr. Antiochos that petitioner has seropositive RA. (Ex. 25, p. 1.) In this report he provided for the first time an explanation of how in his view the flu vaccine can cause (or contribute to) RA. (*Id*. at 3.) Respondent filed responsive reports by both of his experts, who both continued to opine that the flu vaccine cannot cause RA. (ECF No. 46; Exs. F-G.)

On February 7, 2020, the special master issued an order reviewing the expert reports filed to date and urging petitioner and Dr. Gershwin to review a prior case in which she had found the petitioner had failed to prove that the flu vaccine can cause RA. (ECF No. 47 (discussing *C.P. v. Sec'y of Health & Human Servs*., No. 14-917V, 2019 WL 5483624, at *28 (Fed Cl. Spec. Mstr. Aug. 21, 2019).) Petitioner then filed two further reports by Dr. Gershwin, one responding to respondent's most recent expert reports and one responding to the special master's reference to *C.P*. (ECF Nos. 49-50; Exs. 27-29.)

[5] Petitioner initially filed an amended petition on January 30, 2019, alleging that the flu vaccine caused both RA and reactive arthritis. However, the special master ordered petitioner to strike and refile the amended petition to clarify the injury alleged. The amended petition was refiled on October 9, 2019, alleging reactive arthritis only.

Petitioner then requested an entitlement hearing and also filed a final report by Dr. Gershwin responding to specific points raised by the special master (Exs. 30-31) and further medical records (Exs. 33-34.). (ECF Nos. 52-54, 59.) The special master set an entitlement hearing to commence on May 10, 2022; however, the case was subsequently reassigned to the undersigned on September 16, 2021. (ECF No. 61.) The next day I issued a prehearing order and confirmed that the hearing would proceed as previously scheduled. (ECF No. 62.)

However, petitioner subsequently advised on March 28, 2022, that both he and his expert declined to testify. Specifically, petitioner refused to appear at the hearing voluntarily and his expert in turn declined to appear voluntarily if petitioner did not testify. (ECF No. 70.) On March 29, 2022, I issued a follow up order explaining to petitioner that I remain amenable to holding the hearing if the parties choose, but that I otherwise conclude the case is appropriate for resolution on the written record pursuant to Vaccine Rule 8(d). Therefore, I advised that I did not see any need to *sua sponte* compel testimony from petitioner or his expert.[6] (ECF No. 69.) I ordered the parties to confer regarding several points and to file a joint status report responding to my order. (*Id*.) In a joint status report filed by petitioner on March 30, 2022, the parties confirmed the following points as prompted by my order: that petitioner's witnesses would not appear voluntarily; that respondent does not intend to subpoena petitioner's witnesses; and that neither party objects to proceeding via a ruling on the written record. (ECF No. 70.)

Petitioner filed a motion for a ruling on the written record on June 21, 2022. (ECF No. 71.) Respondent filed his response on August 22, 2022. (ECF No. 72.) Petitioner filed no reply. Accordingly, this case is now ripe for resolution. I have concluded that the parties have had a full and fair opportunity to develop the record and that it is appropriate to resolve this case without an entitlement hearing. S*ee Kreizenbeck v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (citing *Simanski v. Sec'y of Health & Human Servs*., 671 F.3d 1368, 1385 (Fed. Cir. 2012); *Jay v. Sec'y of Dept. of Health & Human Servs.*, 998 F.2d 979, 983 (Fed. Cir. 1993.)); *see also* Vaccine Rule 8(d); Vaccine Rule 3(b)(2).

III. Any Claim for Reactive Arthritis is Not Preponderantly Supported

Petitioner's motion for a ruling on the written record advances an argument with respect to RA only, as pleaded in his original petition, and does not argue that he has met his burden of proof with respect to reactive arthritis, as pleaded in his amended petition. (ECF No. 71.) However, there are some references to the possibility of reactive arthritis in petitioner's medical records and he never rescinded his amended petition alleging reactive arthritis. Accordingly, I briefly confirm in the interest of

[6] I also advised petitioner that his affidavit will be less compelling than oral testimony given the lack of cross examination and further that if petitioner's affidavit is silent as to any factual dispute of which respondent has put him on notice, I would entertain a request from respondent for an adverse inference. (ECF No. 70.)

completeness that there is not preponderant evidence that petitioner suffered reactive arthritis.

The expert opinions proffered in this case are unanimous in concluding that petitioner suffered RA and not reactive arthritis.[7] Additionally, as described in greater detail in the Factual History below, although petitioner's medical records include some suspicion of reactive arthritis, he was never diagnosed by any of his treating physicians as experiencing reactive arthritis and was instead diagnosed as having RA. For these reasons, there is not preponderant evidence that petitioner suffered reactive arthritis and it is therefore not necessary to further address that aspect of Dr. Gershwin's opinion that posits that the flu vaccine can cause reactive arthritis or that it did in this case. Although reactive arthritis and RA are both immune-mediated inflammatory conditions and can have overlapping clinical presentations, Dr. Gershwin has been very clear throughout his reports in describing the conditions as involving two distinct disease processes and the evidence presented with respect to the potential for vaccine-causation of each condition is different.

Accordingly, the remainder of this decision will focus on petitioner's claim of vaccine-caused RA.[8]

[7] As explained above, although Dr. Gershwin initially opined that petitioner suffered vaccine-caused reactive arthritis, he reversed that opinion as of his third report and agreed that petitioner suffered RA. (Ex. 25.) Although Dr. Gershwin did not explicitly disclaim his prior opinion as to reactive arthritis, it is clear from Dr. Gershwin's first three reports that he treats the two diagnoses as mutually exclusive explanations of petitioner's history. (Exs. 16-17, 25.) Nor does petitioner's motion for a ruling on the written record in any way suggest that Dr. Gershwin's initial opinion regarding reactive arthritis remains an active consideration in light of his subsequent opinion as to RA. Petitioner's motion makes no request that he be found entitled to compensation for an injury of reactive arthritis nor includes any argument that would support such a finding. (ECF No. 71.)

[8] The Federal Circuit has concluded that it is "appropriate for the special master to first determine what injury, if any, [is] supported by the evidence presented in the record before applying the *Althen* test to determine causation." *Lombardi v. Sec'y of Health & Human Servs.*, 656 F.3d 1343, 1351–53 (Fed. Cir. 2011). Importantly, "the function of a special master is not to 'diagnose' vaccine-related injuries, but instead to determine 'based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the [petitioner]'s injury.'" *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1382 (Fed. Cir. 2009) (quoting *Knudsen ex rel. Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994)). Petitioner must "specify his vaccine-related injury and shoulder the burden of proof on causation." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). "Although the Vaccine Act does not require absolute precision, it does require the petitioner to establish an injury – the Act specifically creates a claim for compensation for 'vaccine-related injury or death.'" *Stillwell v. Sec'y of Health & Human Servs.*, 118 Fed. Cl. 47, 56 (2014) (emphasis omitted) (quoting 42 U.S.C. § 300aa–11(c)). And, in any event, a petitioner must prove by a preponderance of the evidence the factual circumstances surrounding his claim. *See* 42 US.C. § 300aa–13(a)(1)(A).

IV. Factual History

On September 3, 2015, petitioner received the flu vaccination at issue. (Ex. 1, p. 1.) He was 73 at the time and had a history of Type II diabetes, hyperlipidemia, and hypertension. (Ex. 2, p. 6.) He was a heavy smoker until 1999. (Ex. 5, p. 8.)

In his affidavit, petitioner indicates that he began experiencing shoulder pain immediately following his vaccination that increased in intensity over the next 24-hours and that over the ensuing two months he "began to experience severe swelling in my feet and the pain spread to my thumbs, the back of my head, shooting behind my right ear, my abdomen, knees, hands, ankles, and jaw. By October of 2015, I began to experience continuous excruciating pain throughout my whole body, as well as severe weakness and the inability to get out of bed or a chair." (Ex. 9, p. 1.)

On September 7, 2015, four days post-vaccination, petitioner presented to his primary care provider complaining of chronic, intermittent thumb pain in both hands that began more than two and a half years earlier after falling onto his hands. (Ex. 2, pp. 2-7.) He was instructed to treat with over-the-counter pain medication along with warm and cold compresses. (*Id*. at 3-7.) He returned the next day for treatment of pain related to a contusion following an accidental jaw injury. X-rays were negative and Ibuprofen and icing were the only treatment recommendations. (*Id*. at 8-12.) Two days after that, petitioner presented for his annual physical. He was diagnosed with osteoarthritis[9] of the hands and referred to an orthopedist. (Ex. 3, pp. 50-54.)

On September 16, 2015, petitioner presented to an orthopedist. (Ex. 10, pp. 6-7.) Petitioner complained of bilateral hand pain, mostly of the thumbs, but also over the 5th metacarpal (*i.e*. the pinky finger) of the right hand. (Ex. 10, p. 6.) He explained that he had suffered a left side industrial accident in 1965 wherein his hand was crushed and had also previously had right trigger thumb surgery performed. (*Id*.) X-rays showed, *inter alia*, deformities consistent with prior fractures bilaterally as well as stage four arthritis of both thumbs. (*Id.*) The orthopedist attributed petitioner's symptoms to his preexisting arthritis and deformities except for the right pinky finger pain for which "his subjective complaints were out of proportion to objective findings." (*Id*. at 7.) The medical records do not identify whether the pain in petitioner's pinky finger had any separate date of onset.

On September 24, 2015, petitioner presented to the emergency department. (Ex. 3, pp. 40-46.) He reported left arm pain, bilateral thumb pain, bilateral lower extremity pain, and right-sided neck pain and stiffness. (*Id.* at 40.) Petitioner reported that he had been feeling "progressively more sick" since receiving his flu vaccination. (*Id*.) He complained of hand swelling and shortness of breath with exertion. (*Id*.) After

[9] Distinct from the RA at issue in this case, osteoarthritis is "a noninflammatory degenerative joint disease seen mainly in older persons, characterized by degeneration of the articular cartilage, hypertrophy of bone at the margins, and changes in the synovial membrane." *Osteoarthritis,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=35780 (last visited August 15, 2023).

ruling out any life-threatening conditions, he was discharged with a recommendation to follow up with his primary care provider. (*Id*. at 43.) On October 5, 2015, petitioner returned to his primary care provider complaining of neck pain and leg edema for four weeks. (Ex. 3, p. 37.) He was diagnosed with venous insufficiency for which compression stockings were recommended. He was instructed to follow up with an orthopedist regarding the neck pain. (*Id.*)

On October 16, 2015, petitioner presented to a new orthopedist with a complaint of neck pain radiating to his right ear following his flu shot. (Ex. 6, p. 1.) He also complained of hand and foot swelling as well as stomach pain. (*Id*.) X-ray of his cervical spine showed some degenerative changes and petitioner was diagnosed with cervical strain with bridging osteophytes. (*Id*.) Physical therapy was recommended. (*Id*.) On October 23, 2015, petitioner presented to a gastroenterologist. (Ex. 4, p. 7.) He was diagnosed with abdominal pain of unclear etiology. A CT scan of the abdomen was performed on November 4, 2015, and was unremarkable. (*Id*. at 3.)

Petitioner returned to the emergency department on November 30, 2015, and was admitted to inpatient care. (Ex. 3, p. 28-30.) He complained of worsening body aches, fatigue, generalized weakness, lower extremity edema, and difficulty standing. He indicated onset was on September 9, 2015, following his flu vaccination. (*Id*.) Once petitioner was admitted, he had a rheumatology workup.

At this point, petitioner tested positive for rheumatoid factor ("RF"). Additionally, two markers of inflammation, ESR[10] and CRP[11], were also elevated. (Ex. 11, pp. 27, 58.) However, a further marker of RA – Cyclic Citrullinated Peptide antibodies ("CCP")[12] – was negative. (Ex. 11, p. 155.) He was also negative for HLA-B27, a genetic marker frequently found in RA patients. (*Id*.) Overall, petitioner's history and exam was "suggestive for inflammatory arthritis." (Ex. 11, p. 58.) More specifically, it was noted that "[c]linical symptoms [were] highly suspicious for relapsing rheumatoid arthritis although reactive arthritis from viral infection versus reaction from flu vaccine remains a possibility." (*Id*.) An additional notation indicated "possibly RA must [rule out]

[10] "Erythrocyte Sedimentation Rate ("ESR") is the rate at which" red blood cells precipitate out from blood. An elevated rate is evidence of an active inflammatory disease. *Erythrocyte Sedimentation Rate,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=102146 (last visited August 15, 2023).

[11] "C-Reactive Protein" ("CRP") is "the most predominate of the acute-phase proteins." *C-Reactive Protein,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=100489 (last visited August 15, 2023). Acute phase proteins are "processes that occur after the onset of infection, trauma, inflammatory processes, and some malignant conditions." *Acute Phase Response,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=103669 (last visited August 15, 2023).

[12] "Cyclic Citrullinated Peptide" ("CCP") is defined as "a synthetic, citrulline-containing peptide with a cyclic structure, used in assays for rheumatoid arthritis; the presence of antibodies to this peptide is highly specific for rheumatoid arthritis." *Cyclic Citrullinated Peptide*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=97140&searchterm=cyclic+citrullinated+peptide (last visited August 24, 2023).

reactive or post-infectious arthritis since [status post] flu shot." (*Id*. at 62.) During his hospitalization, he had consultation with rheumatologist James Paolino, M.D., who similarly recorded an impression of "[a]cute polyarthritis x 6-8 weeks. Appearance of RA, but the history of vaccine preceding onset. R/O Reactive or post-infectious arthritis. Lab essential for differential dx." (*Id*. at 70; *see also* Ex. 8, p. 9.) Petitioner experienced "remarkable improvement" with steroid treatment and was discharged on December 3, 2015, with a diagnosis of "rheumatoid arthritis flare." (*Id*. at 8.)

Petitioner has continued to treat his RA ever since. However, the subsequent course of petitioner's RA is mostly not germane to the issues presented by petitioner's motion or the parties' experts and is therefore not summarized, except for two specific considerations raised by the experts. First, petitioner was subsequently retested for RF and CCP. Second, petitioner received several further flu vaccinations without incident. Petitioner's RF was rechecked on June 5, 2017, and was substantially higher than when initially tested.[13] (Ex. 8, p. 11.) Petitioner was retested for CCP on October 24, 2019. At that time, he had 73 units where anything over 59 units was considered a "strong positive." (Ex. 24, pp. 3-4.) Petitioner received subsequent flu vaccinations on October 1, 2016, October 1, 2017, and October 1, 2018. (Ex. 22, pp. 13, 37.) It also does not appear that Petitioner's physicians connected any RA flare ups to these subsequent vaccinations.

V. Expert Opinions

a. Petitioner's Rheumatology/Immunology Expert, Dr. Gershwin[14]

In total, Dr. Gershwin provided six reports in this case. (Exs. 16, 17, 25, 27, 29, 30.) As discussed above, Dr. Gershwin's first two reports addressed reactive arthritis rather than RA. Additionally, Dr. Gershwin's fifth report is dedicated to discussing the theory presented in a different case. (Ex. 29.) Accordingly, these three reports are less helpful and are not summarized, though they have been reviewed and considered in full. (Exs. 16-17.)

In his third report, Dr. Gershwin agrees based upon the October 2019 finding of CCP antibodies that petitioner has seropositive RA. (Ex. 25, p. 1.) However, even with this change of opinion regarding diagnosis, he stands by his assertion from his prior

[13] In June of 2017, petitioner's RF measured 261 IU/mL where anything over 14 IU/mL was abnormal. (Ex. 8, p. 11.) When RF was measured in December of 2015, it was 27 IU/mL. (Ex. 11, p. 58.)

[14] Dr. Gershwin is currently a distinguished professor of medicine and the Jack and Donald Chia Professor of Medicine in the Rheumatology/Allergy and Clinical Immunology division of the University of California at Davis, where he previously served as chairperson of the Graduate Group in Immunology. (Ex. 35, p. 1.) Dr. Gershwin received his bachelor's degree from Syracuse University and his master's degree from the Centre for Astrophysics and Supercomputing. (*Id*.) He received his Doctor of Medicine from Stanford University and is currently licensed to practice medicine in California. (*Id.* at 1-2.) Dr. Gershwin is board certified in Internal Medicine with a subspecialty in Rheumatology and in Allergy and Clinical Immunology. (*Id.* at 1-2.) In addition, he has published 72 books and monographs, 1039 experimental papers, 164 book chapters, 277 reviews, 40 guest editorials and book reviews, and five letters to the editors. (*Id.* at 8-138.)

reports that petitioner developed an acute inflammatory arthropathy that was not present prior to vaccination. (*Id*.) Specifically, Dr. Gershwin asserts that, although petitioner is an older individual with other musculoskeletal issues, he did not have any clinical evidence of RA until December 1, 2015, when tests showed elevated inflammatory markers of ESR and CRP.[15] (*Id*. at 2 (citing Ex. 11, p. 27).) Further to this, Dr. Gershwin indicates that petitioner's later lab findings, including an increase in RF and the first detection of CCP in October of 2019, show "significant maturation" or "expansion" as compared to his December 1, 2015 evaluation. (*Id*. at 1-2.) Thus, Dr. Gershwin opines that "one can trace backwards the origin of his antibodies to CCP to the very beginning of his illness, which is shortly after his vaccination." (*Id*. at 1-2.) Although the mechanism is not known, Dr. Gershwin indicates that the presence of CCP antibodies has been shown to correlate to disease severity and are likely related to disease pathology. (*Id*. at 2.)

Dr. Gershwin acknowledges that petitioner was at increased risk of developing RA due to his history of smoking. However, he explains that for at-risk individuals a pre-clinical phase can occur in multiple stages up to the point where accumulating environmental risk factors result in a breach of immune self-tolerance. (*Id*.) Dr. Gershwin suggests that there is increasing evidence that rheumatoid factor is not caused by a single environmental stimulus. Thus, he hypothesizes that "[t]he immunization would be considered the final straw in the multi-step pathogenesis of [RA]." (*Id*. at 3.) Dr. Gershwin cites prior publications discussing several case reports as support for this specific proposition. (*Id*.) In fact, in his fourth report he further stresses that he is not opining that petitioner's RA is "solely" due to his vaccination. (Ex. 27, p. 1.) Dr. Gershwin's fourth report further explains that cytokines produced post-vaccination are pro-inflammatory and "would be key players in the differentiation and expansion of the pathogenic antibodies." (*Id*. at 2.) Dr. Gershwin cites several papers for the proposition that the flu vaccine produces significant levels of cytokines and that vaccination elicits a strong bystander effect. (*Id*.)

Dr. Gershwin stresses that petitioner had no evidence of CCP antibodies prior to vaccination, had no evidence of clinical rheumatoid arthritis prior to vaccination, and developed seropositive RA over the course of several years, with all inflammatory markers dating back to December 1, 2015. (Ex. 25, pp. 2-3.) He also notes that onset of RA at petitioner's older age of 65 is relatively unusual. (*Id*. at 3.) All of this points to the vaccination at issue being the environmental stimulus that broke self-tolerance in petitioner's case. (*Id*.) In his fourth report, Dr. Gershwin further stresses that petitioner's development of anti-CCP antibodies after clinical manifestation is unusual in itself. (Ex. 27, p. 1.) Additionally, Dr. Gershwin suggests that smoking – the other environmental factor implicated by petitioner's medical history – directly produces antibodies to CCP. Therefore, if smoking were the only environmental factor at issue, one would have expected to see the CCP antibodies at the time of diagnosis. (*Id*. at 2.)

[15] As discussed in greater detail under *Althen* prong three, Dr. Gershwin's first report had identified a period of onset for reactive arthritis as occurring between October 1 and October 15, 2015. (Ex. 16, p 4.)

In his final report, Dr. Gershwin answers several specific questions prompted by the special master. He opines that there is no significance in the fact that petitioner later had additional vaccinations without any aggravation of his condition. (Ex. 30, p. 1.) He suggests that the etiologies responsible for initiating a disease are not the same as the etiologies that determine disease activity. He suggests that once self-tolerance is broken, antibody levels do not correlate to the peptides that lead to synovitis and they are not monitored as a biomarker of disease activity. (*Id*.) He further opines that it does not matter whether the vaccine at issue is either live or adjuvanted and that "[t]he only important feature is that it must be antigenic and induce an immune response." (*Id*. at 2.) In response to the special master's concern that large studies have shown the flu vaccine to be safe for RA patients, Dr. Gershwin asserts that the variations in genetic susceptibility, coupled with the need for multiple environmental factors needed to produce disease, effectively place the issue beyond the reach of epidemiology absent better biomarkers. (*Id.*)

b. Respondent's Rheumatology Expert, Dr. Antiochos[16]

Dr. Antiochos provided three reports in this case. His first two reports need not be belabored in light of Dr. Gershwin's change of opinion. (Exs. A, E.) These reports are largely dedicated to affirming the accuracy of petitioner's RA diagnosis. Dr. Antiochos opines that petitioner presented for care in late 2015 with an inflammatory symmetric polyarthritis in a pattern consistent with RA. (Ex. A, p. 5.) Importantly, however, Dr. Antiochos contends that this renders vaccine-causation less likely as compared to Dr. Gershwin's explanation relative to reactive arthritis. According to Dr. Antiochos, the pathogenesis of RA is less established than for reactive arthritis. (*Id*.) Additionally, he stresses that population-based studies have provided a "strong record" with respect to the safety of the flu vaccine in patients with RA. (*Id*.) Accordingly, Dr. Antiochos opines that [w]hile RA became clinically apparent at a date that followed the administration of the influenza vaccine, I find no reason to believe that the influenza vaccine played a causal role in RA development." (*Id*. at 6.)

Dr. Antiochos's third report disagrees with Dr. Gershwin's theory that the flu vaccine can cause RA. (Ex. G.) In short, Dr. Antiochos contends that any role for the flu vaccine in causing RA is refuted by available epidemiologic data that shows no increased risk of developing either incipient RA or enhanced RA disease activity following influenza vaccination. (*Id*. at 1.) Dr. Antiochos stresses that vaccination is a frequent event and RA is not a rare diagnosis. Accordingly, he notes that it is "inevitable" that at least some cases of RA will have onset following vaccination by chance alone. (*Id*. at 2.)

[16] Dr. Antiochos is an assistant professor at John Hopkins University School of Medicine, Division of Rheumatology. (Ex. B, p. 1.) He received his medical degree from Dartmouth Medical School. (*Id.*) He completed his residency in internal medicine at Oregon Health and Science University and a fellowship in rheumatology at Johns Hopkins. (*Id.*) He is currently certified in internal medicine by the Maryland Medical Board. (*Id.* at 3.) In addition, he is board certified in internal medicine and rheumatology and internal medicine by the American Board of Internal Medicine. (*Id.*) He has published 14 original research articles, book chapters, and review articles. (*Id.* at 1-2.)

c. Respondent's Immunology Expert, Dr. Morel[17]

Dr. Morel provided two reports in this case. Despite Dr. Gershwin's initial reliance on reactive arthritis, Dr. Morel opined that a RA diagnosis is instead favored because petitioner was RF positive, these RF factors have been increasing since diagnosis, and in petitioner's most recent recorded visit, he was experiencing a flare of RA with elevated ESR and increased symptoms. (Ex. C, p. 5.) Thus, Dr. Morel's first report does include extensive discussion of the immunology underlying RA. She opines that there is not sufficient evidence to implicate the flu vaccine as a cause of RA. (Ex. C.) Dr. Morel's second report revisited this subject in response to Dr. Gershwin's later assertion that the flu vaccine can cause RA. (Ex. F.)

Dr. Morel explains in her first report that the development of autoimmunity in RA occurs in stages. (Ex. C, p. 3.) The first stage occurs when genetic and environmental factors lead to the generation of auto-reactive T and B cells, often manifesting circulating auto-antibodies. This represents a pre-clinical state that can last for months to years. Thereafter, a further signal, such as micro-trauma, vascular events, or infection, is likely required to initiate clinical RA during which inflammatory Th17 cells or immune complexes initiate synovitis and joint damage. (*Id*.) Dr. Morel opines that "close to 50% of the risk for developing RA is genetic." (*Id.*) She notes that none of the large studies available have supported the hypothesis that the influenza vaccine could be one of the triggers of RA and season influenza vaccines are given to millions of people and are considered extremely safe. (*Id.* at p. 4) She thus concludes that there is no evidence to support the notion that season influenza vaccines could have caused RA in petitioner's case. (*Id.*)

In Dr. Morel's supplemental report, she addresses Dr. Gershwin's theory that petitioner is indeed suffering from RA which was precipitated by the flu vaccine he received in September 2015. (Ex. F, p. 1.) Dr. Morel rejects Dr. Gershwin's view that the vaccination was the final environmental stimulus that led to his RA. (*Id.*) While Dr. Morel agrees that petitioner developed RA in December 2015, she disagrees that the vaccine played a role in causing petitioner's RA. (*Id.* at 2.) To support this conclusion, Dr. Morel notes that there is no evidence in the literature to support the claim that the influenza vaccine can cause RA and that the American College of Rheumatologists recommends that all patients with RA receive influenza vaccines. (*Id.*) In addition, Dr. Morel notes that petitioner has continued to receive annual influenza vaccines with no additional adverse effects. (*Id.*) Therefore, Dr. Morel opines that Petitioner's RA was not caused by the influenza vaccine. (*Id.*)

[17] Dr. Penelope A. Morel is a professor at the University of Pittsburgh in both the Department of Immunology and Division of Rheumatology. (Ex. D, p. 3.) She received her doctorate degree from the University of Geneva. (*Id.* at 1.) She has published 69 refereed articles, 93 published abstracts, and 38 other articles chapters, and reviews. (*Id.* at 4-21.)

VI. Analysis

a. *Althen* Prong One

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citations omitted). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 549. Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu*, 569 F.3d at 1378-79 (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Boatmon*, 941 F.3d at 1359 (quoting *Knudsen*, 35 F.3d at 548-49).

In this case, there is no dispute that RA is an autoimmune condition of uncertain cause that generally involves a combination of genetic and environmental factors or stimuli progressively leading to autoimmunity over a prolonged preclinical phase. (Ex. A, p. 5; Ex. C, p. 3; Ex. 25-2, p. 3.) Petitioner argues that Dr. Gershwin's explanation of how a flu vaccine can cause the final loss of autoimmune self-tolerance in RA carries his burden of proof. (ECF No. 71, pp. 10-11.) Specifically, petitioner relies on Dr. Gershwin's explanation that the flu vaccine produces cytokines which contribute to the expansion of pathogenic autoantibodies due to a strong bystander effect. (*Id*. at 11.) Respondent counters that Dr. Gershwin's explanation is both unsupported and too vague, especially when contrasted against contrary epidemiology and the current views of the relevant scientific community, which do not consider the flu vaccine to be among the environmental stimuli capable of causing RA. (ECF No. 72, pp. 17-20.) Respondent is far more persuasive on the whole. Very little on this record apart from Dr. Gershwin's say-so associates any vaccine with RA whereas much more purports to refute Dr. Gershwin's opinion.

Dr. Gershwin did present a 2007 review paper regarding the pathogenesis of RA that indicates that vaccinations have been considered as a "possible" environmental trigger of "various diseases," but this is not specific to RA and stands in contrast to the much firmer links the authors draw to other environmental triggers for RA. (Gourley & Miller, *Mechanisms of Disease: Environmental Factors in the Pathogenesis of Rheumatic Disease*, 3 NATURE CLINICAL PRACTICE RHEUMATOLOGY 172, 177 (2007) *(*Ex. 32, p. 6).) Otherwise, of all the literature Dr. Gershwin cites, only two papers from the late 1980s and early 1990s discuss case reports and case series of RA developing post vaccination. (DPM Symmons & K Chakravarty, *Can Immunisation Trigger Rheumatoid Arthritis?*, 52 ANNALS RHEUMATIC DISEASES 843, (1993) *(*Ex. 26M); ASM Jawad & DGJ Scott, *Immunisation Triggering Rheumatoid Arthritis?,* 48 ANNUALS RHEUMATIC DISEASES 174, (1989) (EX. 26N).) However, even those papers address different vaccines, mostly

tetanus-containing vaccines.[18] The Symmons paper cites a single case of reported arthritis following flu vaccination, but specifies that the subject did not meet the criteria for a diagnosis of RA. (Symmons & Charkravarty, *supra*, at Ex. 26M, p. 1.) Respondent also filed several additional case reports of RA following vaccination, precisely because Dr. Morel stresses that the limited number of available case reports stands in contrast to much larger studies that have not supported the hypothesis. (Ex. C, p. 4; Gurjot Basra, Praveen Jojoria, & Emilio Gonzalez, *Rheumatoid Arthritis and Swine Influenza Vaccine: A Case Report,* 2012 CASE REPORTS IN RHEUMATOLOGY 1, (2012) (Ex. C, Tab 19); (Maria Antonia Pou et al., *Development of Autoimmune Diseases After Vaccination,* 14 J. CLINICAL RHEUMATOLOGY 243, (2008) (Ex. C, Tab 20); Tabache et al., *Acute Polyarthritis after Influenza A Immunization*, 78 JOINT BONE SPINE 319, 321 (2011) (Ex. C, Tab 21, p. 3).)

Petitioners in this program often highlight the usefulness of case reports in cases of rare diseases or unusual occurrences. *E.g. Patton v. Sec'y of Health & Human Servs.*, 157 Fed. Cl. 159, 166-67 (2021). However, case reports "'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value'. . . ," even though they are not entirely devoid of evidentiary value. *Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011), *aff'd*, 786 F.3d 1373 (Fed. Cir. 2015)); *see also Crutchfield v. Sec'y of Health & Human Servs.*, No. 09-39V, 2014 WL 1665227, at *19 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) ("single case reports of Disease X occurring after Factor Y . . . do not offer strong evidence that the *temporal* relationship is a *causal* one—the temporal relationship could be pure random chance"), *aff'd*, 125 Fed. Cl. 251 (2014). In this case, neither the Jawad nor Symmons papers cited by Dr. Gershwin are particularly strong evidence. Jawad presents a single anecdotal case report. (Jawad & Scott, *supra,* at Ex. 26N.) Symmons discusses several prior case series in brief but then discusses several significant reasons for doubting any causal relationship. (Symmons & Charkravarty, *supra*, at Ex. 26M.) In fact, Dr. Gershwin himself refers to the Symmons and Jawad paper as "not themselves proof" but as "rais[ing] the specter of proof of principle." (Ex. 25, p. 3.) However, this mere "specter" must be considered in light of the fact that subsequent investigation, as documented in numerous more recent papers filed in this case, has provided little that would bear out the hypothesis.

Respondent's experts have come forward with a number of more recent epidemiologic studies of varying size that weigh against Dr. Gershwin's theory. Specifically: Carola Bardage et al., *Neurological and Autoimmune Disorders After Vaccination Against Pandemic Influenza A (H1N1) with a Monovalent Adjuvanted Vaccine: Population Based Cohort Study in Stockholm, Sweden,* 343 BRIT. MED. J. 1, (2011) *(*Ex. A, Tab 1) (examined the risk of neurological and autoimmune disorders in people vaccinated against influenza A in the population of those registered in Stockholm county on October 1, 2009 who had lived in the region since January 1, 1998 and were

[18] In his final report Dr. Gershwin does suggest that his theory would apply to any vaccine with "the only requirement obviously [being] that it is antigenic and induces an immune response," but this only underscores respondent's charge of vagueness as discussed further below. (Ex. 30, p. 2.)

vaccinated against H1N1 and found no change in the risk for rheumatoid arthritis); F. Milanetti et al., *Safety and Immunogenicity of Co-Administered MF 59-Adjuvanted 2009 Pandemic and Plain 200-10 Seasonal Influenza Vaccines in Rheumatoid Arthritis Patients on Biologicals,* 177 CLINICAL AND EXPERIMENTAL IMMUNOLOGY 287, (2014) (Ex. A, Tab 2) (seeking to determine the safety and immunogenicity of co-administered non-adjuvated seasonal and pandemic influenza vaccines in 30 RA patients and concluded that simultaneous administration of adjuvanted pandemic and non-adjuvated seasonal influenza vaccines are safe and highly immunogenic in RA patients); Milomir Milanovic et al., *Influenza Vaccination in Autoimmune Rheumatic Disease Patients*, 229 TOHOKU J. EXPERIMENTAL MED. 29, (2013) (Ex. A, Tab 3) (studying the effect of vaccinating annually for influenza using trivalent inactivated split vaccine during 2006-2010 on patients suffering from autoimmune rheumatic diseases and found no exacerbation of the underlying disease); Paula Ray et al., *Risk of Rheumatoid Arthritis Following Vaccination with Tetanus, Influenza and Hepatitis B Vaccines Among Persons 15-59 Years of Age,* 29 VACCINE 6592, (2011) (Ex. A, Tab 5) (compared rates of new-onset RA between one million vaccinated and unvaccinated Kaiser Permanente Northern California members from 1997-1999 and found a possible association between RA and the influenza vaccine in a smaller cohort analysis that was not borne out by the larger case-control analysis); Ljudmila Stojanovich, *Influenza Vaccination of Patients with Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA),* 13 CLINICAL AND DEV. IMMUNOLOGY 373, (2006) (Ex. A, Tab 7) (studied 54 RA patients, half of which received the influenza vaccine while the other half did not, and found the vaccine was tolerated well in all cases and those RA patients who were vaccinated had fewer occurrences of infections); Fabrizio Conti, Soheila Rezai, & Guido Valesini, *Vaccination and Autoimmune Rheumatic Diseases,* 8 AUTOIMMUNITY REV. 124, 126(2008) (Ex. C, Tab 29, p. 3) (RA patients immunization against the influenza can be considered safe and immunogenic in most cases). The Federal Circuit has previously stressed that a petitioner is not obligated to present an epidemiological case supporting his claim. *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325 (Fed. Cir. 2006). However, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory." *D'Tiole v. Sec'y of Health & Human Servs.*, 726 F. App'x 809, 811 (Fed. Cir. 2018) (citing *Andreu*, 569 F.3d at 1379 ("Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the Special Master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.").

Dr. Gershwin offers no specific critique of any of the studies cited by respondent's experts, but urges more generally that the complicated relationship between RA and its environmental factors makes it a poor fit for epidemiologic study. (Ex. 30, p. 2.) While this might be a somewhat reasonable caveat, it is not enough to cast substantial doubt on the value of the studies in this record without a more direct discussion of study methodology and limitations. Dr. Gershwin cites a paper by Gourley and Miller on this point, but that paper only suggests the epidemiology in this context is challenging and requires a large population. (Gourley & Miller, *supra,* at Ex. 32.) It

does not cast doubt on all epidemiology relative to RA and does not specifically address prior studies regarding vaccination. Moreover, other literature cited by petitioner in this case indicates that there are environmental factors such as smoking, air pollution, silica exposure, and infection, that are accepted as having associations with RA despite the issues raised by Dr. Gershwin. (*E.g*. V. Michael Holers et al., *Rheumatoid Arthritis and the Mucosal Origins Hypothesis: External Protection Becomes Internal Destruction*, 14 NATURE REV. RHEUMATOLOGY 542, 546 (2018) (Ex. 28A, p. 5); Kevin D. Deane, Jill M. Norris, & V. Michel Holers, *Pre-Clinical Rheumatoid Arthritis: Identification, Evaluation and Future Directions for Investigation,* 36 RHEUMATOLOGY DISEASE CLINICS N. AM. 213, 216 (2010) (Ex. 28B, p. 4).) Even if one did entirely discount the epidemiologic studies themselves, Dr. Gershwin's theory also stands in contrast to the evidence of record demonstrating that the relevant medical community recommends that RA patients receive the flu vaccine. (Jasvinder A. Singh et al., *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis*, 68 ARTHRITIS & RHEUMATOLOGY 1, 18 (2015) (Ex A, Tab 6, p. 18); S van Assen, *EULAR Recommendations for Vaccination in Adult Patients with Autoimmune Inflammatory Rheumatic Diseases,* 40 ANNUALS RHEUMATOLOGY DISEASES 414, 416 (2011) (Ex. A, Tab 8, p. 3).)

None of this indicates that Dr. Gershwin's theory should be viewed as impossible. However, respondent is also persuasive in contending that, especially when considering this overall context, Dr. Gershwin's explanation is incredibly vague. Much of what Dr. Gershwin discusses in his reports relates to the broader understanding that RA is an autoimmune condition that develops in a stepwise process in response to a combination of genetic and environmental factors. (Ex. 25, p. 3.) Little in this broader discussion is disputed. Indeed, it is very similar to Dr. Morel's discussion of the immunology underlying RA. (Ex. C, pp. 3-4.) However, Dr. Gershwin's broader explanation of RA autoimmunity does not in itself implicate vaccines as one of the environmental stimuli contributing to RA. Those aspects of Dr. Gershwin's theory that are vaccine-specific, namely his discussion of post-vaccinal cytokines and bystander activation, lack any tether to RA and appear disjointed from the remainder of his causal explanation.

With regard to the ability of the flu vaccine's ability to generate pro-inflammatory cytokines, Dr. Gershwin cites Talaat, et al. (Ex. 27, p. 2 (citing Talaat et al., *supra*, at Ex. 28D).) In that study, 20 healthy subjects received a trivalent influenza vaccination and serum cytokine levels were measured for up to two weeks post-vaccination. Several cytokines were elevated post-vaccination; however, only mild adverse reactions were reported.[19] Nothing in this paper suggests that the observed cytokines would cause or contribute to RA specifically or autoimmunity generally. Dr. Gershwin combines the Talaat study with four additional papers he suggests show vaccines generally have a "strong bystander effect." (Ex. 27, p. 2 (citing Susan van Aaist et al.,

[19] Ten subjects had generalized myalgia, eight reported injection site pain, two subjects reported episodes of diaphoresis, one had sore throat, one experienced vomiting, and one had a vasovagal event during a blood draw. (Talaat et al., *Rapid Changes in Serum Cytokines and Chemokines in Response to Inactivated Influenza Vaccination*, 12 INFLUENZA AND OTHER RESPIRATORY VIRUSES 202 (2017) (Ex. 28D.))

Bystander Activation of Irrelevant CD4⁺ T Cells Following Antigen-Specific Vaccination Occurs in the Presence and Absence of Adjuvant, 12 PLOS ONE 1, (2017) (Ex. 28E); Gianfranco Di Genova et al., *Bystander Stimulation of Activated CD4⁺ T Cells of Unrelated Specificity Following a Booster Vaccination with Tetanus Toxoid,* 40 EUR. J. IMMUNOLOGY 976, (2010) (Ex. 28F), Eleonora Li Causi et al., *Vaccination Expands Antigen-Specific CD4⁺ Memory T Cells and Mobilizes Bystander Central Memory T Cells*, 10 PLOS ONE 1, (2015) (Ex. 28G); Melody A. Swartz, Jeffrey A. Hubbell, & Sai T. Reddy, *Lymphatic Drainage Function and Its Immunological Implications: From Dendritic Cell Homing to Vaccine Design,* 20 SEMINARS IN IMMUNOLOGY 147, (2008) (Ex. 28H).) Dr. Gershwin suggests that following vaccination, proinflammatory cytokines would "be key players in the differentiation and expansion of pathogenic autoantibodies." (*Id*.) Because Dr. Gershwin does not explain his reliance on any of these specific studies, he has not substantiated *how* they support his opinion. Three of these studies (Li Causi, et al., *supra,* at Ex. 28G; van Aaist, et al., *supra,* at Ex. 28E; and Di Genova, et al., *supra,* at Ex. 28F) appear only to address the preliminary question of whether vaccines induce bystander activation *at all* while the fourth (Swartz, et al., *supra,* at Ex. 28H) is limited to discussing lymphatic drainage post-vaccination. None of these studies involves RA specifically or otherwise demonstrate bystander activation as leading to human disease more broadly.

Importantly, even if one accepts Dr. Gershwin's explanation of cytokine-driven, post-vaccination bystander activation as a generally useful concept, its particular application to RA would still be unsupported. Dr. Morel agrees that transition to clinical RA *might* involve a "second signal" that ultimately produces joint damage following an inflammatory cascade. However, she explains that micro-trauma, vascular events, and infectious events, but not vaccines, are suggested as viable possibilities. (Ex. C, p. 4.) Additionally, the medical literature Dr. Gershwin himself relies upon in this case also indicates that his underlying premise – that a distinct environmental stimulus acts as the "final straw" in the multi-step process of transitioning from preclinical to clinical RA – is unsettled. Specifically, the literature indicates that

> [W]hile genetic and environmental factors have been associated with RA, the exact role that these factors play in the development of RA-related autoimmunity is not yet clear. Also, it is unclear whether these factors may lead to initial RA related immune dysregulation or transition from asymptomatic autoimmunity to clinically-apparent RA.

(Deane, Norris, & Holers, *supra,* at Ex. 28B, p. 4; *see also* Elizabeth W. Karlson & Kevin Deane *Environmental and Gene-Environment Interactions and Risk of Rheumatoid Arthritis,* 38 RHEUMATOLOGY DISEASE CLINICS N. AM. 405, 405 (2012) (Ex. 26I, p. 1) ("the growing understanding of the prolonged period prior to the first onset of symptoms of RA suggests that these environmental and genetic factors are likely acting to drive the development of RA-related autoimmunity long before the appearance of the first joint symptoms and clinical findings that are characteristic of RA."); (Holers et al., *supra,* at Ex. 28, p. 5) ("very few long-term prospective studies have been performed whose goal would be to understand how stage-specific exposures influence the initial pre-clinical

development of RA-related autoimmunity and subsequent clinical and/or immune transitions.") Thus, even if bystander activation showed that vaccines could be considered capable of causing or contributing to the type of immune dysregulation involved in the development of RA, it would still remain to be established that vaccines, or in fact any environmental factor otherwise associated with RA, would act in the manner of a "final straw" as Dr. Gershwin proposes.

Petitioner stresses in his motion that "[i]t is not necessary for a petitioner to point to conclusive evidence in the medical literature linking a vaccine to the petitioner's injury, so long as the petitioner can show by a preponderance of the evidence that there is a causal relationship between the vaccine and the injury, whatever the details of the mechanism may be." (ECF No. 71, pp. 11-12 (citing *Moberly v Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1325 (Fed Cir. 2010).) However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. denied*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. Appx. 999 (Fed. Cir. 2013).

In this case, Dr. Gershwin has presented a description of the autoimmune process involved in RA that does not itself implicate vaccines, a separate concept by which any vaccine might in general contribute to autoimmunity without respect to any specific context, and precious little that could tie the two together. This would *at best* set the stage for the proposed causal relationship to be possible. (*E.g*. Gourley & Miller, *supra,* at Ex. 32, p. 6 (RA review article discussing vaccine as only a "possible" environmental trigger for "various diseases").) Without more it simply does not add up to preponderant evidence showing that the flu vaccine can cause or contribute to RA. *Boatmon*, 941 F.3d at 1360 (explaining that "a 'plausible' or 'possible' theory does not satisfy the standard"). Moreover, given that respondent has filed substantial literature casting doubt on the idea that the flu vaccine causes or contributes to RA, and given that both parties have filed literature demonstrating that vaccines are not generally viewed as among the accepted environmental factors contributing to RA, even that mere possibility would be at most a remote one. Accordingly, the analytic gap is simply too great to allow for acceptance of Dr. Gershwin's theory.

In light of all of the above, Dr. Gershwin has not presented a sound and reliable theory of causation in this case and petitioner has not met his preponderant burden of proof under *Althen* prong one.

a. *Althen* Prong Two

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*,

956 F.2d at 1148. In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1280) (stating that "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'"). However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) (stating that "there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). Ultimately, petitioner may support his claim either through his medical records or by expert opinion. § 300aa-13(a)(1).

There is no dispute in this case that petitioner's RA first manifested clinically at some point in the months following his vaccination, though there is a seeming inability to pinpoint any precise onset. As discussed below under *Althen* prong three, Dr. Gershwin provides a range of possibilities from late September to early December of 2015. Dr. Antiochos agrees on respondent's behalf that his condition first manifested in late 2015. (Ex. A, p. 5.) Dr. Morel places onset in December of 2015. (Ex. F, p. 2.) However, for all the reasons discussed separately under *Althen* prongs one and three, there is not preponderant evidence supporting this post-vaccination onset of symptoms as medically significant. And, in any event, temporality alone would not meet petitioner's burden of proof under *Althen* prong two. *See, e.g. Bangerter v. Sec'y of Health and Human Servs.,* No. 15-1186V, 2022 WL 439535, at *28 (Fed. Cl. Spec. Mstr. Jan. 18, 2022 (citing *Veryzer v. Sec'y of Health and Human Servs.,* 100 Fed. Cl. 344, 356 (2011).

Petitioner's treating physicians were largely silent as to causation. Petitioner relies on the medical record of his treating rheumatologist (Dr. Paolino) as support for the idea that there is a logical sequence of cause and effect between his vaccination and onset of his RA, but misconstrues the record. (ECF No. 71, pp. 13-15 (citing Ex. 8, p. 9.) Dr. Paolino's impression on December 1, 2015 was "Acute polyarthritis x 6-8 weeks. Appearance of RA, but the history of vaccine preceding onset. R/O reactive or post-infectious arthritis." (Ex. 8, p. 9.) Petitioner quotes only the first part of this impression, leaving out the language with respect to ruling out other conditions, and interprets this record as an opinion that petitioner's RA was vaccine-caused. (ECF No. 71, p. 13.) However, this record reflects that Dr. Paolino is engaging in differential diagnosis based on petitioner's history and presentation, not setting forth any opinion or theory of causation. When read in full it is clear that Dr. Paolino is recording a diagnostic suspicion for RA (the "appearance of RA"), but is also concerned that the temporality to vaccination should point to another condition, such as the reactive arthritis initially posited by petitioner's own expert, that should be ruled out before concluding that petitioner does suffer RA. Dr. Gershwin's first two reports confirm that

an opinion that vaccines can cause reactive arthritis is *not* equivalent to an opinion that they can cause RA. (Exs. 16, 17.)

Additionally, as Dr. Morel has raised, petitioner's physicians continued to recommend flu vaccinations and petitioner continued to receive those vaccinations without any adverse effects. (Ex. F, p. 1; Ex. 22, pp. 13, 37.) This is consistent with the standard of care for RA. (Singh et al., *supra*, at Ex A, Tab 6, p. 18; van Assen et al., *supra,* at Ex. A, Tab 8, p. 3.) Although Dr. Gershwin indicates his hypothesis distinguishes events that break self-tolerance from events that determine the course of the disease (Ex. 30, p. 2), the fact that petitioner's treating physicians felt administration of the flu vaccine was safe and appropriate is some evidence in itself. "A treating physician's decision to administer or withhold a vaccination can be highly probative of causation." *Tarsell v. United States*, 133 Fed Cl. 782, 797 (2017) (citing *Andreu,* 569 F.3d at 1376).)

Dr. Gershwin asserts that the petitioner's lab results show a progression over time that allows for the markers of his disease to be traced back to onset and thereby evidence vaccine causation. (Ex. 25 p. 1-2.) Specifically, petitioner's second RF test of 261 U/mL showed an increase in RF after nearly two years and his CCP test of 73 units was positive for the first time in October 2019, four years after onset, despite having been previously negative at the time of onset. (*Id.* p. 2; Ex. 8, p. 11; Ex. 24, pp. 3-4.) Although it is true that petitioner's tests reflected these changes, Dr. Gershwin has not substantiated that this is evidence meaningful to causation.

The literature filed in this case suggests that production of antibodies during the pre-clinical phase does correlate to disease severity; however, the production of antibodies is not in itself essential for clinical disease. (Markus M. J. Nielen et al., *Specific Autoantibodies Precede the Symptoms of Rheumatoid Arthritis: A Study of Serial Measurements in Blood Donors,* 50 ARTHRITIS & RHEUMATISM 380, 385 (2004) (Ex. 26D, p. 6.); Gary S. Firestein & Iain B. McInnes, *Immunopathogenesis of Rheumatoid Arthritis,* 46 IMMUNITY 184, 184 (2017) (Ex. C, Tab 3, p. 1); V.F.A.M. Derksen, T.W.J. Huizinga, & D. van der Woude, *The Role of Autoantibodies in the Pathophysiology of Rheumatoid Arthritis,* 39 SEMINARS IMMUNOPATHOLOGY 437, 437 (2017) (Ex C, Tab 5, p. 1).) "[C]onversion to RF seropositivity continued after the onset of symptoms and reached the commonly reported prevalence level of 67% after 6 years." (*Id*.) In this case, petitioner was RF seropositive from the first time he was tested. Although the same literature notes that "[i]n the majority of patients, seropositivity, once established, is stable" (Nielen et al., *supra,* at Ex. 26D, p. 6.), nothing on this record indicates that petitioner's subsequent rise in RF is informative with respect to either the timing of his initial seroconversion or the cause of his condition. Additionally, the literature indicates that some studies have shown a subset of subjects develop CCP antibodies after transitioning to clinical RA. (Lars Klareskog et al., *Mechanisms of Disease: Genetic Susceptibility and Environmental Triggers in the Development of Rheumatoid Arthritis,* 2 NATURE CLINICAL PRAC.: RHEUMATOLOGY 425, 428 (2006) (Ex. C, Tab 10, p. 4).) Dr. Gershwin has also filed literature explaining that "the utility of anti-CCP retesting during the disease course in patients present with

inflammatory arthritis is actually questionable and not recommended . . . the clinical value of anti-CCP levels at disease onset and influence of titer changes over time on disease outcome have not been fully clarified." (Nicola Bizzaro et al., *Anti-Cyclic Citrullinated Peptide Antibody Titer Predicts Time to Rheumatoid Arthritis Onset in Patients with Undifferentiated Arthritis: Results from a 2-Year Prospective Study,* 15 ARTHRITIS RESEARCH AND THERAPY 1, 2 (2013) (Ex. 31, p. 2).)

Dr. Gershwin also relies on the fact that there is no other evidence of the cause of petitioner's RA, but this fails to account for petitioner's history of smoking. Both parties' experts agree that smoking is well established as a factor contributing to the development of RA. (Ex. 25, p. 2; Ex. C, p.2; Ex. F, p.1.) Given that Dr. Gershwin agrees on this point, he has not adequately addressed why petitioner's history of smoking alone is not explanation enough for his RA. Dr. Gershwin suggests that petitioner's belated CCP finding is incompatible with smoking being the sole environmental contributor because in that context CCP antibodies are expected at the time of diagnosis. (Ex. 27, p. 2.) For this proposition he cites a review by Holers, et al. (*Id*. (citing Holers et al., *supra,* at Ex. 28A).) However, this paper does not support Dr. Gershwin's assertion. Holers, et al., explain that a number of studies have associated smoking with CCP antibodies and the eventual development of RA. (Holers et al., *supra,* at Ex. 28A, p. 5.) On the whole, these studies support a "well-accepted association" between heavy smoking and the risk of developing seropositive RA. (*Id*.) But none of the study findings discussed indicate that CCP antibodies are necessarily present at the time of diagnosis. In fact, one of the cited studies found that smoking was associated with both seropositive and seronegative RA. (*Id*.) Despite the association, the authors indicate that "[t]he exact stage-specific timing of smoking effects during the pre-clinical to classified arthritis natural history of RA is not well understood." (*Id*.)

In light of all of the above, petitioner has not met his preponderant burden of proof under *Althen* prong two.

b. *Althen* Prong Three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30,

2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

As discussed under *Althen* prong one, there is not agreement on whether the environmental factors that contribute to clinical RA operate at earlier points within the preclinical disease process or as the final set piece as Dr. Gershwin opines. (*Compare* Ex. 27, p. 2 (proposing post-vaccination cytokines as "the final environmental block that leads to the clinical onset of disease" *and* Deane, Norris, & Holers, *supra,* at Ex. 28B, p. 4; *see also* Holers et al., *supra,* at Ex. 28A, p. 5.) Thus, it does not even appear possible to identify any clearly defined beginning point of a relevant latency period. However, even accepting *arguendo* that a vaccine could be the "final straw" in the development of RA, Dr. Gershwin's opinion is still unpersuasive. Petitioner asserts that onset of his RA began sometime between October 1, 2015, and October 15, 2015. (ECF No. 71, p. 14.) He further contends that a latency of between four to six weeks post-vaccination is appropriate to demonstrate a proximate temporal relationship between the influenza vaccination and development of RA. (*Id*.) For both of these points, petitioner cites the final page of Dr. Gershwin's first report. (*Id*. (citing Ex. 16, p. 4.) However, petitioner's reliance on this aspect of Dr. Gershwin's opinion is not clear-cut.

Initially, Dr. Gershwin identified the first concerning change in petitioner's arthritic symptoms as occurring on September 24, 2015, without respect to diagnosis. (Ex. 16, p. 1.) Later in the same report, he specifically indicated that petitioner suffered onset of *reactive arthritis* sometime between October 1 and October 15, 2015. (*Id*. 4.) These two statements alone are difficult to reconcile, even accounting for Dr. Gershwin's suggestion that determining onset is more difficult due to other underlying medical conditions. (*Id.*) It is not clear how Dr. Gershwin arrived at the specific October 1-October 15 timeframe. However, in his third report, wherein he changed his diagnostic opinion, Dr. Gershwin opined that "I do not believe [petitioner] had evidence of clinical *rheumatoid arthritis* until the presence of the elevated inflammatory markers of ESR and CRP on December 1, 2015." (Ex. 25, p. 2 (emphasis added).) Dr. Morel then agreed that this is the point at which petitioner developed clinical RA.[20] (Ex. F, p. 1.) Depending on which of Dr. Gershwin's statements controls, the latency from vaccination to injury is anywhere from three weeks to just shy of nine weeks. Yet, among all of his reports, Dr. Gershwin only ever specifically endorses a period of four-to-six weeks as consistent with any theory he has presented.

Further muddying the waters, while the clinical signs of RA and reactive arthritis may overlap, Dr. Gershwin was very clear in describing two distinct causal mechanisms for reactive arthritis and RA respectively. The full extent of Dr. Gershwin's explanation of the appropriate timing in any of his reports is that onset occurring four to six weeks

[20] Dr. Gershwin does indicate that the presentations of reactive arthritis and RA can be confused, which may suggest Dr. Gershwin intended to cite December 1 as the point by which RA could be diagnosed as opposed to the date it became clinical RA. (Ex. 16, p.4.) However, this is not necessarily clear from the report. Even granting that assumption, it would still not be clear how the specific diagnosis of RA interplays with Dr. Gershwin's stated inability to otherwise identify a precise onset of symptoms due to other underlying conditions.

post-vaccination is "consistent with the development of a T cell response." (Ex. 16, p. 4.) But this was articulated relative to reactive arthritis specifically. (*Id*.) In his first report, he explained that reactive arthritis is distinguished by the fact that it involves a non-specific inflammatory T cell response that would occur de novo post-vaccination and does not include a role for autoantibodies. (Ex. 16, p. 3.) In contrast, he explains in his later reports that vaccine causation of RA would involve a necessary autoantibody response, but in the context of an already smoldering autoimmune process. (Ex. 25, p. 2; Ex. 27, p. 2.) It is possible that these distinctions could ultimately have no net significance to timing; however, there is no basis for making that assumption on this record and Dr. Gershwin has provided no separate explanation regarding the timeframe for the post-vaccination portion of the overall development of autoimmunity in RA.

Even looking beyond what Dr. Gershwin makes explicit, none of the limited literature that Dr. Gershwin cites on this record with specific regard to suspected post-vaccinal RA provides support for a four-to-six week latency for RA. The Jawad case report had a latency of three weeks. (Jawad & Scott, *supra*, at Ex. 26N.) The Symmons paper largely did not specify onset periods. The only case series with a confirmed period of onset indicated that post-vaccination arthralgia occurred between 7-10 days post-vaccination. (Symmons & Chakravarty, *supra*, at Ex. 26M, p. 1.) The case reports filed by respondent had onset periods of between four days and one week following H1N1 influenza vaccination and three days after a tetanus booster vaccination. (Basra, Jajoria, & Gozalez, *supra,* at Ex. C, Tab 19; Maria Antonia Pou et al., *supra,* at Ex. C, Tab 20; Tabache et al., *supra,* at Ex. C, Tab 21.) Even accounting for the mechanistic aspects of Dr. Gershwin's theory, the study he cited regarding post-vaccination cytokines indicated that these cytokines peak at 24 hours post vaccination and the study he cited with respect to bystander activation showed that in human subjects T cell expansion peaked at one-week post-vaccination. (Talaat et al., *supra,* at Ex. 28D; Causi et al., *supra,* at Ex. 28G, p. 5.) All of this implies a shorter latency than what petitioner and Dr. Gershwin cite. None of it precludes a longer latency, but in the absence of further explanation by Dr. Gershwin, it does not support one either.

In light of all of the above, petitioner has not met his preponderant burden under *Althen* prong three.

VII. Conclusion

Petitioner has clearly suffered and he has my sympathy. However, for all the reasons discussed herein, petitioner has not preponderantly demonstrated that he actually suffered a vaccine-caused injury and is therefore not entitled to compensation. Accordingly, this case is dismissed.[21]

[21] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master